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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/740,256	12/18/2003	James E. Dahlberg	FORS-08497	1902

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EXAMINER	
BABIC, CHRISTOPHER M	
ART UNIT	**PAPER NUMBER**
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/740,256	DAHLBERG ET AL.	
	Examiner	Art Unit	
	Christopher M. Babic	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-34,36 and 39-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-34, 36, and 39-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 6, 2006 has been entered. Claim(s) 32-34, 36, and 39-82 are pending.

Claim Rejections - 35 USC § 112 - 2nd Paragraph

The previous rejections of claim(s) 32-34, 36, and 39-82 have been withdrawn in view of Applicant's amendment.

Applicant's amendment(s) necessitated the following new ground(s) of rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim(s) 32-34, 36, and 39-82 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claim(s) 32 and 57 are indefinite because it is unclear what structure is detected within step (c). Step (a) requires that **all** "RNA detection structures" have a microRNA and an unlabeled probe, however, step (b) requires the dissociation of **all** the mircroRNA(s) from the probe(s) thereby leaving no "RNA detection structures," as defined by the claim. Thus, it is unclear what "RNA detection structures" are to be detected in step (c). It is noted that the claim does not require a certain order of steps, thus the claim can be interpreted such that step (c) occurs before step (b), in which case the claim does not appear to be indefinite. However, since the claim can be interpreted such that step (c) is to occur after step (b), the method as a whole remains indefinite for that particular embodiment.

(b) Claim(s) 81 and 82 are further indefinite because it is unclear which unlabeled probe, i.e. the first or the second, is to be dissociated from the microRNA.

Appropriate clarification is required.

Claim Rejections - 35 USC § 103

The previous rejection(s) of claims over Dattagupta in view of the applied secondary references are withdrawn in view of Applicants' amendments.

Applicant's amendment(s) necessitated the following new ground(s) of rejection.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claim(s) 32, 33, 47-52, 54, 57, 58, 60, 62, 71-76, and 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi et al. (U.S. 5,118,801) in view of Lau et al. ("An Abundant Class of Tiny RNAs with Probable Regulatory Roles in *Caenorhabditis elegans*. Science. 26 October 2001. Vol. 294: Pages 858-862).

As noted above, claim(s) 32 and 57 are indefinite because it is unclear what structure is detected within step (c). For the purpose(s) of this rejection, the claim is interpreted such that one element, i.e. either the unlabeled probe or microRNA target of the "RNA detection structure" can be detected.

Furthermore, the claim does not require a certain order of steps, thus the claim can be interpreted such that step (c) occurs before step (b) or vice versa. For the purpose(s) of this rejection, the claim is interpreted such that step (b) occurs before step (c).

Lizardi teaches a method (fig. 4-5; col. 11-12, ex. 2, for example) comprising: a) contacting RNA (col. 9, lines 60-65, for example) with an unlabeled probe to form an RNA detection structure (fig. 5, for example), wherein

said probe comprises a first region that is complementary to said RNA and a second region that is not complementary to said RNA (fig. 5, for example), wherein a first portion of said second region is complementary to a second portion of said second region, wherein said first portion and said second portion can hybridize to each other when said probe is hybridized to said RNA (fig. 5, for example); b) disassociating said RNA from said unlabeled probe (col. 11, lines 60-end, for example); and, c) detecting formation of said RNA detection structure through an amplification reaction (col. 12, lines 1-5, for example). Lizardi does not expressly disclose microRNA detection.

With regard to claim(s) 47, 58, 60, 71, Lizardi teaches incubation with a polymerase within an amplification reaction (col. 9-11, example I, for example).

Lau provides a supporting disclosure that teaches two types of short RNAs, both about 21 to 25 nucleotides (21-25 nt) in length (lin-4 and let-7) (i.e. microRNA (miRNA)) (abstract; table 1, for example), an obvious structurally equivalent species of the genus molecule RNA. Lau further teaches the detection of miRNAs (fig. 3, for example) as well as the motivation to study these molecules, as their abundance implies that they function in a variety of regulatory pathways.

With regard to claim(s) 33, 48-50, 62, and 72-74 Lau expressly teaches quantitating microRNA and distinguishing unique microRNA from another nucleic acid in a cell lysate sample (fig. 3, for example).

With regard to claim(s) 51, 52, 75, and 76 Lau expressly teaches a plurality of different miRNAs 21-22 nucleotides in length (fig. 3; table 1, for example).

With regard to claim(s) 54 and 78, Lau expressly teaches Let-7 miRNA (abstract; table 1, for example).

It would have been *prima facie obvious* to a practitioner of ordinary skill in the art to apply the RNA detection methods of Lizardi to microRNA, an obvious structurally equivalent species of the genus molecule RNA since Lau suggests the detection and further study of these molecules because their abundance implies that they function in a variety of regulatory pathways.

2. Claim(s) 32, 33, 39, 40, 48-52, 54, and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lane et al. (U.S. 5,770,365) in view of Lau et al. ("An Abundant Class of Tiny RNAs with Probable Regulatory Roles in *Caenorhabditis elegans*. Science. 26 October 2001. Vol. 294: Pages 858-862).

As noted above, claim(s) 32 is indefinite because it is unclear what structure is detected within step (c). For the purpose(s) of this rejection, the claim is interpreted such that one element, i.e. either the unlabeled probe or microRNA target of the "RNA detection structure" can be detected.

Furthermore, the claim does not require a certain order of steps, thus the claim can be interpreted such that step (c) occurs before step (b) or vice versa.

For the purpose(s) of this rejection, the claim is interpreted such that step (b) occurs before step (c).

Lane teaches a method (fig. 1-4; col. 4-13, ex. 2, for example) comprising: a) contacting RNA (col. 4, lines 30-40, for example) with an unlabeled probe to form an RNA detection structure (fig. 1-4, for example), wherein said probe comprises a first region that is complementary to said RNA and a second region that is not complementary to said RNA (fig. 1-4, for example), wherein a first portion of said second region is complementary to a second portion of said second region, wherein said first portion and said second portion can hybridize to each other when said probe is hybridized to said RNA (fig. 1-4, for example); b) disassociating said RNA from said unlabeled probe (col. 10, lines 30-55, for example); and, c) detecting formation of said RNA detection structure through an amplification reaction (col. 11-13, lines 1-5, for example). Lizardi does not expressly disclose microRNA detection.

With regard to claim(s) 39 and 40, Lane teaches fluorescent probes (col. 11-13, lines 1-5, for example).

Lau provides a supporting disclosure that teaches two types of short RNAs, both about 21 to 25 nucleotides (21-25 nt) in length (lin-4 and let-7) (i.e. microRNA (miRNA)) (abstract; table 1, for example), an obvious structurally equivalent species of the genus molecule RNA. Lau further teaches the detection of miRNAs (fig. 3, for example) as well as the motivation to study these molecules, as their abundance implies that they function in a variety of regulatory pathways.

With regard to claim(s) 33 and 48-50, Lau expressly teaches quantitating microRNA and distinguishing unique microRNA from another nucleic acid in a cell lysate sample (fig. 3, for example).

With regard to claim(s) 51 and 52, Lau expressly teaches a plurality of different miRNAs 21-22 nucleotides in length (fig. 3; table 1, for example).

With regard to claim(s) 54, Lau expressly teaches Let-7 miRNA (abstract; table 1, for example).

It would have been *prima facie obvious* to a practitioner of ordinary skill in the art to apply the RNA detection methods of Lane to microRNA, an obvious structurally equivalent species of the genus molecule RNA since Lau suggests the detection and further study of these molecules because their abundance implies that they function in a variety of regulatory pathways.

3. Claim(s) 34 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi et al. (U.S. 5,118,801) in view of Lau et al. ("An Abundant Class of Tiny RNAs with Probable Regulatory Roles in *Caenorhabditis elegans*. Science. 26 October 2001. Vol. 294: Pages 858-862) as applied to claim(s) 32, 33, 47-52, 54, 57, 58, 60, 62, 71-76, and 78 above, and in further view of Prudent et al. (U.S. 5,985,557).

With regard to claim(s) 34 and 61, the methods of Lizardi have been outlined in above rejections. Lizardi does not specifically disclose a detection procedure that includes forming an invasive cleavage structure, cleaving said

invasive cleavage structure, and detecting the cleavage of said invasive cleavage structure.

Prudent provides a supporting disclosure that teaches target nucleic acid detection that includes forming an invasive cleavage structure (fig. 16A-E, Figure 29, for example), cleaving said invasive cleavage structure (col. 31-39, example III, for example), and detecting the cleavage of said invasive cleavage structure (col. 31-39, example III, for example). They further disclose that the invader-directed or "invasive" cleavage assay is useful in the detection and quantification of individual variants or alleles in a mixed sample population (col. 38, lines 15-60).

It would have been *prima facie obvious* to a practitioner of ordinary skill in the art to incorporate detection procedures of Prudent into the methods of Lizardi since Prudent suggests such a modification to aid in the detection and quantification of individual variants or alleles in a mixed sample population.

4. Claim(s) 36, 39-41, 44-46, 59, 63-65, and 68-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi et al. (U.S. 5,118,801) in view of Lau et al. ("An Abundant Class of Tiny RNAs with Probable Regulatory Roles in *Caenorhabditis elegans*. Science. 26 October 2001. Vol. 294: Pages 858-862) as applied to claim(s) 32, 33, 47-52, 54, 57, 58, 60, 62, 71-76, and 78 above, and in further view of Morris et al. ("Rapid reverse transcription-PCR detection of hepatitis C virus RNA in serum by using the

TaqMan fluorogenic detection system J Clin Microbiol. 1996 Dec;34(12):2933-6).

With regard to claim(s) 36, 44-47, 59, and 68-71, the methods of Lizardi have been outlined in above rejections. Lizardi does not specifically disclose a detection procedure that includes the polymerase chain reaction (PCR), more specifically, a PCR that utilizes a fluorescent probe configured for FRET detection.

Morris provides a supporting disclosure that teaches TaqMan RT-PCR encompassing the limitations set forth in the above claims (fig. 1; pg. 2934, Materials and Methods, RT-PCR, for example). Furthermore, they teach that in the TaqMan assay post amplification manipulations are reduced therefore offering significant time savings.

It would have been *prima facie obvious* to a practitioner of ordinary skill in the art to incorporate the TaqMan PCR assay disclosed by Morris into the methods of Lizardi since Morris suggests such a modification for significant time savings.

5. Claim(s) 42, 43, 53, 66, 67, and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi et al. (U.S. 5,118,801) in view of Lau et al. ("An Abundant Class of Tiny RNAs with Probable Regulatory Roles in *Caenorhabditis elegans*. Science. 26 October 2001. Vol. 294: Pages

858-862) as applied to claim(s) 32, 33, 47-52, 54, 57, 58, 60, 62, 71-76, and 78 above, and in further view of Marras et al. "Multiplex detection of single-nucleotide variations using molecular beacons" Genet Anal. 1999 Feb;14(5-6):151-6).

With regard to claim(s) 42, 43, 53, 66, 67, and 77, the methods of Lizardi have been outlined in above rejections. Lizardi does not specifically disclose detection procedures that include the use of probes that form different conformations upon hybridization or the detection of polymorphisms.

Marras provides a supporting disclosure that teaches detection of single-nucleotide variants (pg. 154, col. 2, for example) through the incorporation of FRET enabled molecular beacons (fig. 1; pg. 152, col. 2, for example). Furthermore, Marras teaches that molecular beacons are uniquely suited for the detection of single-nucleotide variants because they bind their targets with higher specificity than conventional oligonucleotide probes (pg. 152, col. 1, for example).

It would have been *prima facie obvious* to a practitioner of ordinary skill in the art to incorporate the FRET enabled molecular beacons disclosed by Marras into the methods of Lizardi since Marras suggests such a modification because molecular beacons detect polymorphisms with higher specificity than conventional oligonucleotide probes.

("An Abundant Class of Tiny RNAs with Probable Regulatory Roles in *Caenorhabditis elegans*. Science. 26 October 2001. Vol. 294: Pages 858-862) as applied to claim(s) 32, 33, 47-52, 54, 57, 58, 60, 62, 71-76, and 78 above, and in further view of Hyldig-Nielsin et al. (U.S. 5,985,563).

With regard to claim(s) 55, 56, 79, and 80, the methods of Lizardi have been outlined in above rejections. Lizardi does not specifically disclose the use of peptide nucleic acids (PNAs).

Hyldig-Nielsin et al. disclose an assay using PNA probes (col. 17, lines 30-45; col. 19,20, example 1, for example). They further disclose that PNAs have a higher thermal instability of mismatching bases whereby PNAs exhibit a greater specificity for their complementary nucleic acids than traditionally used nucleic acid probes (col. 2, lines 40-55).

It would have been *prima facie obvious* to a practitioner of ordinary skill in the art to incorporate the FRET enabled molecular beacons disclosed by Hyldig-Nielsin into the methods of Lizardi since Hyldig-Nielsin suggests such a modification because PNA probes exhibit a greater specificity for their complementary nucleic acids than traditionally used nucleic acid probes.

7. Claim(s) 81 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi et al. (U.S. 5,118,801) in view of Lau et al. ("An Abundant Class of Tiny RNAs with Probable Regulatory Roles in *Caenorhabditis elegans*. Science. 26 October 2001. Vol. 294: Pages 858-

862) as applied to claim(s) 32, 33, 47-52, 54, 57, 58, 60, 62, 71-76, and 78 above, and in further view of Barany et al. (U.S. 6,027,889).

With regard to claim(s) 81 and 82, the methods of Lizardi have been outlined in above rejections. Lizardi does not specifically disclose contacting the target RNA with two unlabeled probes.

Barany provides a supporting disclosure that teaches the detection of single point mutations through the use two probes that hybridize adjacent to the nucleotide that is being analyzed within the target sequence i.e. a combined ligation detection reaction and polymerase chain reaction (LDR/PCR) (fig. 8-22; col. 9-11, for example).

It would have been *prima facie obvious* to a practitioner of ordinary skill in the art to design and apply two probes that hybridize adjacent to a nucleotide within the methods of Lizardi since Barany suggests such a modification in order to allow for the detection of single point mutations within a target sequence.

8. Claim(s) 81 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lane et al. (U.S. 5,770,365) in view of Lau et al. ("An Abundant Class of Tiny RNAs with Probable Regulatory Roles in *Caenorhabditis elegans*. Science. 26 October 2001. Vol. 294: Pages 858-862) as applied to claim(s) 32, 33, 39, 40, 48-52, 54, and 81 above, and in further view of Fodor et al. (U.S. 5,968,740).

With regard to claim(s) 81, the methods of Lane have been outlined in above rejections. Lizardi does not specifically disclose contacting the target RNA with two unlabeled probes.

Fodor provides a supporting disclosure that teaches the heat denaturation and rehybridization of target-probe complexes to investigate the duplex temperature melting range of the complexes (fig. 8-22; col. 9-11, for example).

It would have been *prima facie obvious* to a practitioner of ordinary skill in the art to heat denature and rehybridize the target-probe complexes within the methods of Lane since Fodor suggests such a modification in order to investigate the duplex temperature melting range of the complexes.

The above references arrive at the claimed invention because the claim does not require that both nucleic acid probes be hybridized at the same time and therefore, the rehybridization of a second probe encompasses the limitation(s) of claim 81.

Conclusion

Claims 32-34, 36, and 39-82 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 571-272-8507. The examiner can normally be reached on Monday-Friday 7:00AM to 4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

11/5/07

Christopher M. Babic
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1/8/07